PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 12432490/EJH/DYS	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. **PCT/AU2004/000427**	International filing date *(day/month/year)* 2 April 2004	Priority date *(day/month/year)* 3 April 2003
International Patent Classification (IPC) or national classification and IPC **Int. Cl.** [7] A61K 31/47, 31/473; A61P 25/28, 39/04, 39/06		
Applicant PRANA BIOTECHNOLOGY LTD et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [X] *(sent to the applicant and to the International Bureau)* a total of **28** sheets, as follows:
      - [X] sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      - [ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

[X]	Box No. I	Basis of the report
[ ]	Box No. II	Priority
[ ]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of the report
23 December 2004	11 July 2005
Name and mailing address of the IPEA/AU	Authorized Officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	**S. Chew** Telephone No. (02) 6283 2248

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2004/000427

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1 (b))

☐ publication of the international application (under Rule 12.4)

☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

☐ the international application as originally filed/furnished

☒ the description:

pages **1-65** as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

☒ the claims:

pages as originally filed/furnished
pages* as amended (together with any statement) under Article 19
pages***66-93** received by this Authority on **23 December 2004** with the letter of **23 December 2004**
pages* received by this Authority on with the letter of

☒ the drawings:

pages **1/3-3/3** as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	**YES**
	Claims **1-39**	**NO**
Inventive step (IS)	Claims	**YES**
	Claims **1-39**	**NO**
Industrial applicability (IA)	Claims **1-39**	**YES**
	Claims	**NO**

2. Citations and explanations (Rule 70.7)

This report has considered the following documents cited in the International Search Report:

D1 WO 2002/051415

D2 US 6001852

NOVELTY (N): Claims 1-39

D1 discloses the use of clioquinol and phanquinone in treating or preventing prion disorders eg Creutzfeld-Jacob disease and spongiform encephalopathies. It further discloses a list of 8-substituted quinolines (See page 18 line 21 to page 20 line 11) suitable for use in the treatment.

D2 discloses a method for treating or preventing Alzheimer's Disease (AD), a neurological disease resulting from oxidative stress, with clioquinol and optional with vitamin B12. It is also disclosed that the method of the invention prevents or alleviates the signs and symptoms of AD eg cognitive impairment and memory loss (See col. 6 lines 43-48, col. 7 lines 18-31 and claims 1, 3 and 4).

Claims 1, 2 and 16-22 defining the use of any 8-substituted quinolone or an agent which reduces the levels of reactive oxygen species (as in claim 21) in the treatment of a neurological condition or disorder, are anticipated by the disclosures of clioquinol in D1 and D2.

Claims 3-15 and 23-39 are also not novel in the light of the disclosure of D1 which teaches several suitable 8-substituted quinolines which fall within the scope of the compounds envisaged by the claims.

Therefore claims 1-39 lack novelty.

INVENTIVE STEP (IS): Claims 1-39

As above.

INDUSTRIAL APPLICABILITY (IA): Claims 1-39

Claims 1-39 have industrial applicability.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1 and 20 are not clear with regard to the terms " derivative", "homolog", "analog", "chemical equivalent" and "mimetic". It is not clear what compounds are being envisaged by these broad terms.

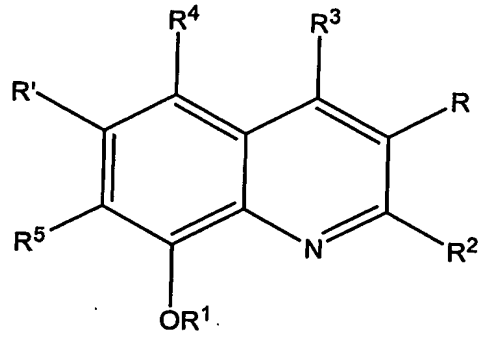
Claim 5 is not clear as it is appended to itself.

CLAIMS

1. A method for the prophylaxis and/or treatment of a condition or disorder associated with or exacerbated by oxidative stress and with symptoms including cognitive impairment or memory loss in a subject, said method comprising administering to said subject an effective amount of an 8-substituted quinolone which reduces the levels of reactive oxygen species or a derivative, homolog, analog, chemical equivalent or mimetic thereof.

2. The method of Claim 1, wherein the condition or disorder is a neurological condition or disorder.

3. The method of Claim 1 or 2, wherein the 8-substituted quinolone is of the Formula I:



I

in which:

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety;

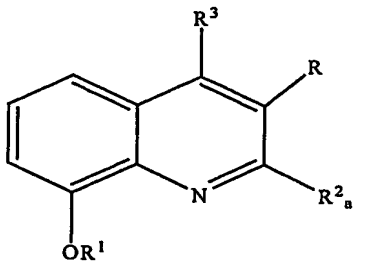
R^2 is H; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted aryl; optionally substituted heterocyclyl; optionally substituted alkoxy; an antioxidant; a targeting moiety; COR^6 or CSR^6 in which R^6 is H, optionally substituted

alkyl, optionally substituted alkenyl, hydroxy, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant, a targeting moiety, OR^7, SR^7 or NR^7R^8 in which R^7 and R^8 are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl or optionally substituted heterocyclyl; CN; $CH_2NR^9R^{10}$, $HCNOR^9$ or $HCNNR^9R^{10}$ in which R^9 and R^{10} are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl or optionally substituted heterocyclyl; OR^{11}, SR^{11} or $NR^{11}R^{12}$ in which R^{11} and R^{12} are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl or optionally substituted heterocyclyl or together form optionally substituted heterocyclyl; or $SO_2NR^{13}R^{14}$ in which R^{13} and R^{14} are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl or optionally substituted heterocyclyl; and

R^3, R^4, R^5, R and R' are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl optionally substituted alkoxy, optionally substituted acyl, hydroxy, alkylamino, alkylthio, alkylsulphonyl, alkylsulphinyl, halo, SO_3H, amine, optionally substituted aryl, optionally substituted heterocyclyl, an anti-oxidant or a targeting moiety,

with the proviso that when R^1 to R^3, R and R' are H, then R^4 is not Cl and R^5 is not I.

4. The method of Claim 1 or 2, wherein the 8-substituted quinolone is of the Formula Ia:



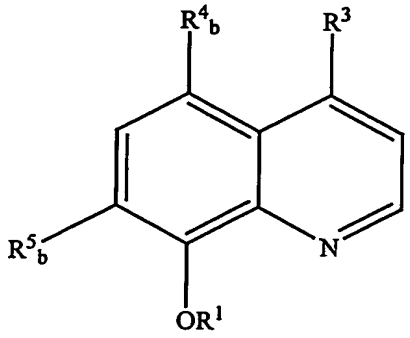
in which:

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety;

R^3 and R are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl optionally substituted alkoxy, optionally substituted acyl, hydroxy, alkylamino, alkylthio, alkylsulphonyl, alkylsulphinyl, halo, SO_3H, amine, optionally substituted aryl, optionally substituted heterocyclyl, an anti-oxidant or a targeting moiety; and

R^2a is H; optionally substituted C_{1-6} alkyl; optionally substituted C_{1-6} alkenyl; optionally substituted aryl; optionally substituted heterocyclyl; an antioxidant; a targeting moiety; COR^6a or CSR^6a in which R^6a is H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, hydroxy, optionally substituted aryl, optionally substituted heterocyclyl or OR^7a, SR^7a or NR^7aR^8a in which R^7a and R^8a are either the same or different and selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted aryl or optionally substituted hetercyclyl; CN; $CH_2NR^9aR^{10}a$, $HCNOR^9a$ or $HCNNR^9aR^{10}$ in which R^9a and $R^{10}a$ are either the same or different and selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted aryl or optionally substituted heterocyclyl; $OR^{11}a$, $SR^{11}a$ or $NR^{11}aR^{12}a$ in which $R^{11}a$ and $R^{12}a$ are either the same or different and selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted aryl or optionally substituted heterocyclyl or together form optionally substituted heterocyclyl; or $SO_2NR^{13}aR^{14}a$ in which $R^{13}a$ and $R^{14}a$ are either the same or different and selected from H or optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted aryl or optionally substituted heterocyclyl.

5. The method of Claim 5, wherein the 8-substituted quinolone is of the Formula Ib:



Ib

in which:

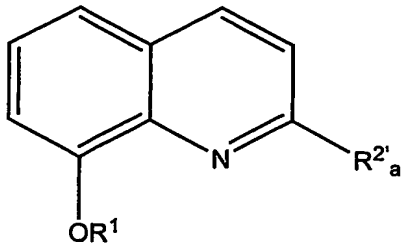
R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety;

R^3 is either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl optionally substituted alkoxy, optionally substituted acyl, hydroxy, alkylamino, alkylthio, alkylsulphonyl, alkylsulphinyl, halo, SO_3H, amine, optionally substituted aryl, optionally substituted heterocyclyl, an anti-oxidant or a targeting moiety; and

R^4b and R^5b are either the same or different and selected from H; optionally substituted C_{1-6} alkyl; optionally substituted C^{2-6} alkenyl; halo; an anti-oxidant; a targeting moiety, SO_3H; $SO_2NR^{13}aR^{14}a$ in which $R^{13}a$ and $R^{14}a$ are as defined in Formula Ia above; or $OR^{15}b$, $SR^{15}b$ or $NR^{15}bR^{16}b$ in which $R^{15}b$ and $R^{16}b$ are either the same or different and selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{1-6} acyl, optionally substituted aryl or optionally substituted heterocyclyl,

with the proviso that when R^1 and R^3 are H, then R^4b is not Cl and R^5b is not I.

6. The method of Claim 4, wherein the Ia is of the Formula of IIa:



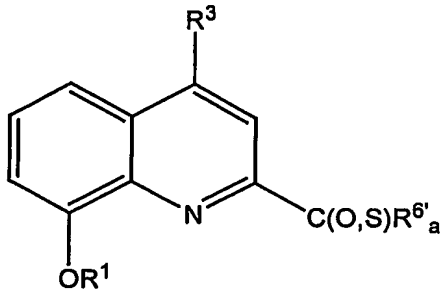
IIa

in which:

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety; and

$R^{2'}a$ is optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted aryl or optionally substituted heterocyclyl.

7. The method of Claim 4, wherein the Ia is of the Formula of IIIa:



IIIa

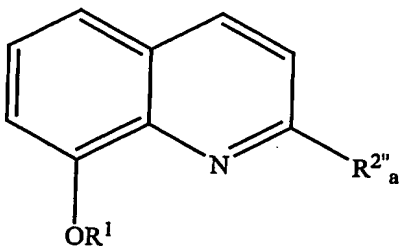
in which:

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety;

R^3 is either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl optionally substituted alkoxy, optionally substituted acyl, hydroxy, alkylamino, alkylthio, alkylsulphonyl, alkylsulphinyl, halo, SO_3H, amine, optionally substituted aryl, optionally substituted heterocyclyl, an anti-oxidant or a targeting moiety; and

$R^{6'}a$ is optionally substituted C_{1-6} alkyl, optionally substituted C2-6 alkenyl, hydroxy, $OR^{7'}a$, $SR^{7'}a$, $N_2R^{7'}aR^{8'}a$ or $NR^{7'}a\ R^{8'}a$ in which $R^{7'}a$ and $R^{8'}a$ are either the same or different and selected from H, optionally substituted C_{1-6} alkyl, optionally substituted aryl or optionally substituted heterocyclyl.

8. The method of Claim 1 or 2, wherein the 8-substituted quinolone is of the Formula IVa;



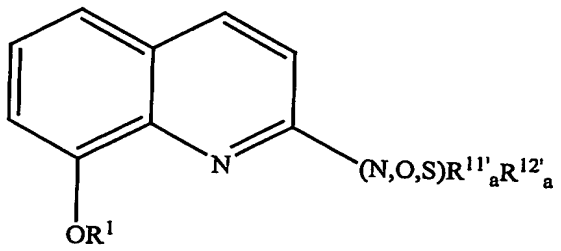
IVa

in which:

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety; and

$R^{2''}a$ is CN; $CH_2NR^{9'}aR^{10'}a$, $HCNOR^{9'}a$ or $HCNNR^{9'}aR^{10'}a$ in which $R^{9'}a$ and $R^{10'}a$ are either the same or different and selected from H, optionally substituted C_{1-6} alkyl, optionally substituted alkenyl, optionally substituted aryl or optionally substituted heterocyclyl.

9. The method of Claim 1 or 2, wherein the 8-substituted quinolone is of the Formula Va;



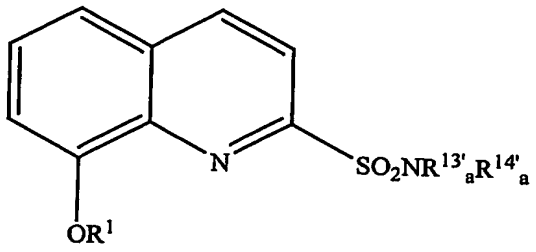
Va

in which:

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety; and

$R^{11}a'$ and $R^{12}a'$ are either the same or different and selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted aryl and optionally substituted heterocyclyl or together form optionally substituted heterocyclyl.

10. The method of Claim 1 or 2, wherein the 8-substituted quinolone is of the Formula VIa;



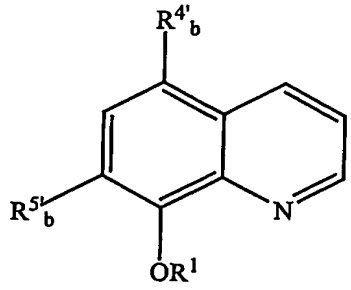
VIa

in which:

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety; and

$R^{13}a'$ and $R^{14}a'$ are either the same or different and selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted aryl or optionally substituted heterocyclyl.

11. The method of Claim 5, wherein the Ib is of the Formula of IIb;



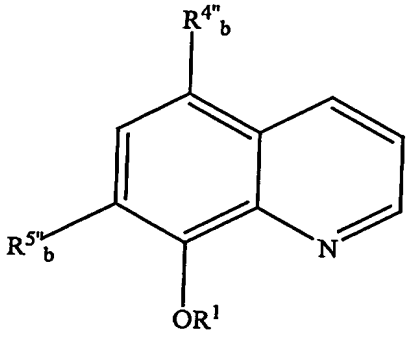
IIb

in which:

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety; and

R^4b' and R^5a' are either the same or different and selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, amine, SO_3H, optionally substituted aryl or optionally substituted heterocyclyl.

12. The method of Claim 5, wherein the Ib is of the Formula of IIIb;



IIIb

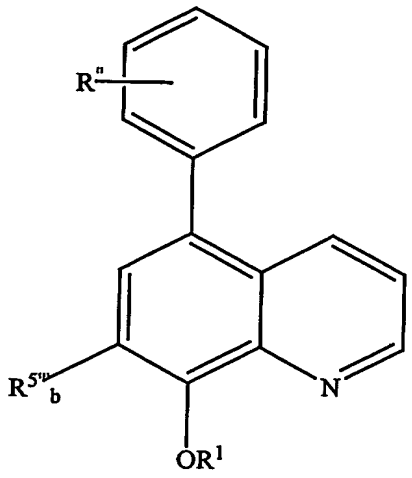
in which

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety;

R^4b'' is H or halo; and

R^5b'' is optionally substituted aryl or optionally substituted heterocyclyl.

13. The method of Claim 1 or 2, wherein the 8-substituted quinolone is of the Formula IVb;



IVb

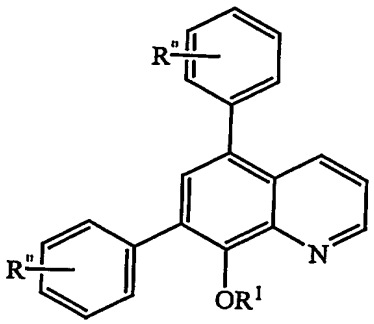
in which:

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety;

R" is C_{1-6} alkoxy, halo, C_{1-6} alkyl, C_{2-6} alkenyl or C_{1-6} haloalkyl; and

R^5b" is H or halo.

14. The method of Claim 1 or 2, wherein the 8-substituted quinolone is of the Formula Vb;



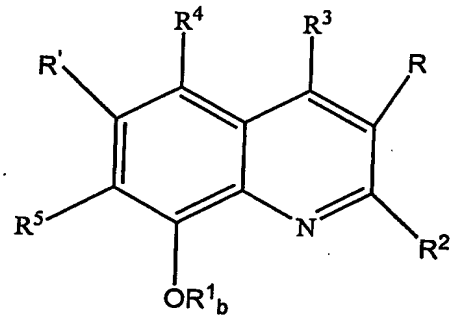
Vb

in which

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety; and

R" is C_{1-6} alkoxy, halo, C_{1-6} alkyl, C_{2-6} alkenyl or C_{1-6} haloalkyl.

15. The method of Claim 1 or 2, wherein the 8-substituted quinolone is of the Formula VIb;



VIb

in which:

R^2 is H; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted

aryl; optionally substituted heterocyclyl; optionally substituted alkoxy; an antioxidant; a targeting moiety; COR^6 or CSR^6 in which R^6 is H, optionally substituted alkyl, optionally substituted alkenyl, hydroxy, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant, a targeting moiety, OR^7, SR^7 or NR^7R^8 in which R^7 and R^8 are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl or optionally substituted heterocyclyl; CN; $CH_2NR^9R^{10}$, $HCNOR^9$ or $HCNNR^9R^{10}$ in which R^9 and R^{10} are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl or optionally substituted heterocyclyl; OR^{11}, SR^{11} or $NR^{11}R^{12}$ in which R^{11} and R^{12} are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl or optionally substituted heterocyclyl or together form optionally substituted heterocyclyl; or $SO_2NR^{13}R^{14}$ in which R^{13} and R^{14} are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl or optionally substituted heterocyclyl; and

R^3, R^4, R^5, R and R' are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl optionally substituted alkoxy, optionally substituted acyl, hydroxy, alkylamino, alkylthio, alkylsulphonyl, alkylsulphinyl, halo, SO_3H, amine, optionally substituted aryl, optionally substituted heterocyclyl, an anti-oxidant or a targeting moiety, with the proviso that when R^1 to R^3, R and R' are H, then R^4 is not Cl and R^5 is not I; and

R^1b" is optionally substituted C_{1-6} alkyl, optionally substituted aryl, optionally substituted aryl acyl, C_{1-6} alkyl acyl or optionally substituted heterocyclyl.

16. The method of Claim 2, wherein the neurological disorder is selected from sporadic or familial AD, Parkinson's disease, multiple sclerosis, amylotrophic lateral sclerosis, epilepsy, drug abuse or drug addiction (alcohol, cocaine, heroin, amphetamine or the like), spinal cord disorders and/or injuries, dystrophy or degeneration of the neural retina (retinopathies) and peripheral neuropathies, such as diabetic neuropathy and/or the

peripheral neuropathies induced by toxins, cardiomyopathy, AIDS dementia and HIV-1 induced neurotoxicity, atherosclerosis, cerebral ischaemia, cerebral palsy, cerebral tumour, chemotherapy-induced organ damage, cisplatin-induced nephrotoxicity, coronary artery bypass surgery, Creutzfeldt-Jacob disease and its new variant associated with "mad cow" disease, Down's syndrome, post-traumatic epilepsy, Friedrich's ataxia, frontotemporal dementia, glaucoma, glomerulopathy, hemochromatosis, hemodialysis, hemolysis, hemolytic uraemic syndrome (Weil's disease), hemorrhagic stroke, Hallerboden-Spatz disease, heart attack and reperfusion injury, Huntington's disease, Lewy body disease, intermittent claudication, ischaemic stroke, inflammatory bowel disease, macular degeneration, malaria, methanol-induced toxicity, meningitis (aseptic and tuberculous), motor neuron disease, multiple system atrophy, myocardial ischaemia, neoplasia, peri-natal asphyxia, Pick's disease, progressive supra-nuclear palsy, radiotherapy-induced organ damage, restenosis after angioplasty, retinopathy, senile dementia, schizophrenia, sepsis, septic shock, spongiform encephalopathies, subharrachnoid hemorrage/cerebral vasospasm, subdural hematoma, surgical trauma, including neurosurgery, thalassemia, transient ischaemic attack (TIA), traumatic brain injury (TBI), traumatic spinal injury, transplantation, vascular dementia, viral meningitis and viral encephalitis, dementia associated with Down's syndrome, amyotrophic lateral sclerosis, motorneuron disease, cataract, dementia with Lewy body formation, diffuse Lewy body disease, neurological diseases resulting from oxidative stress, such as, neurological disease resulting from diabetes, stroke and cardiovascular disease.

17. The method of Claim 2, wherein said agent is administered in conjunction with one or more pharmaceutically acceptable compounds used for treating a neurological disorders.

18. The method of Claim 17, wherein said compound is selected from phenserine, galantamine, or tacrine, Vitamin E or Vitamin C, flurbiprofen or ibuprofen, NCX-2216, 17-β-oestradiol and vitamin B12.

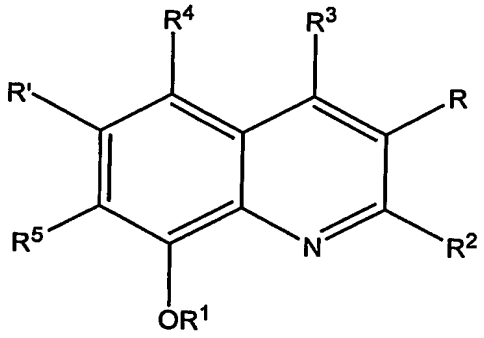
19. Use of any one or more of the agents of the Formulas I, Ia, Ib, IIa, IIIa, IVa, Va, VIa, IIb, IIIb, IVb, Vb and VIb in the manufacture of a medicament for the treatment and/or prophylaxis of a condition or disorder associated with or exacerbated by oxidative stress and with symptoms including cognitive impairment or memory loss.

20. A method for the prophylaxis and/or treatment of mild cognitive impairment (MCI) in a subject, said method comprising administering to said subject an effective amount of an 8-substituted quinolone or a derivative, homolog, analog, chemical equivalent or mimetic thereof which reduces the levels of reactive oxygen species.

21. A method for improving cognitive function or memory in a subject, said method comprising administering to said subject an effective amount of an agent which reduces the levels of reactive oxygen species thereby improving the cognitive function or memory of said subject.

22. The method of Claim 20 or 21, wherein the condition or disorder is a neurological condition or disorder.

23. The method of Claim 20 or 21, wherein the 8-substituted quinolone is of the Formula I:



I

in which:

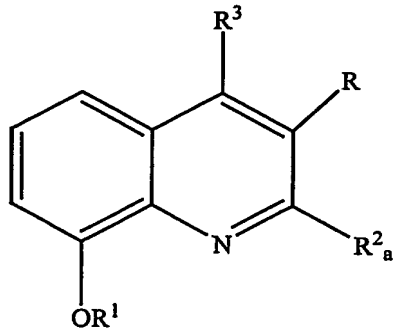
R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety;

R^2 is H; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted aryl; optionally substituted heterocyclyl; optionally substituted alkoxy; an antioxidant; a targeting moiety; COR^6 or CSR^6 in which R^6 is H, optionally substituted alkyl, optionally substituted alkenyl, hydroxy, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant, a targeting moiety, OR^7, SR^7 or NR^7R^8 in which R^7 and R^8 are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl or optionally substituted heterocyclyl; CN; $CH_2NR^9R^{10}$, $HCNOR^9$ or $HCNNR^9R^{10}$ in which R^9 and R^{10} are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl or optionally substituted heterocyclyl; OR^{11}, SR^{11} or $NR^{11}R^{12}$ in which R^{11} and R^{12} are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl or optionally substituted heterocyclyl or together form optionally substituted heterocyclyl; or $SO_2NR^{13}R^{14}$ in which R^{13} and R^{14} are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl or optionally substituted heterocyclyl; and

R^3, R^4, R^5, R and R' are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl optionally substituted alkoxy, optionally substituted acyl, hydroxy, alkylamino, alkylthio, alkylsulphonyl, alkylsulphinyl, halo, SO_3H, amine, optionally substituted aryl, optionally substituted heterocyclyl, an anti-oxidant or a targeting moiety,

with the proviso that when R^1 to R^3, R and R' are H, then R^4 is not Cl and R^5 is not I.

24. The method of Claim 20 or 21, wherein the 8-substituted quinolone is of the Formula Ia:



in which:

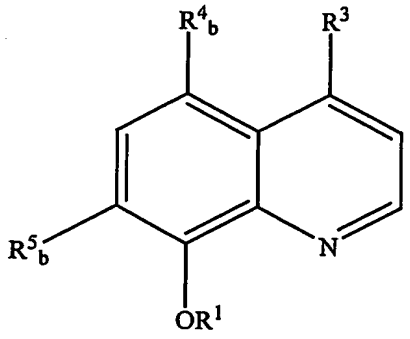
R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety;

R^3 and R are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl optionally substituted alkoxy, optionally substituted acyl, hydroxy, alkylamino, alkylthio, alkylsulphonyl, alkylsulphinyl, halo, SO_3H, amine, optionally substituted aryl, optionally substituted heterocyclyl, an anti-oxidant or a targeting moiety; and

R^2a is H; optionally substituted C_{1-6} alkyl; optionally substituted C_{1-6} alkenyl; optionally substituted aryl; optionally substituted heterocyclyl; an antioxidant; a targeting moiety; COR^6a or CSR^6a in which R^6a is H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, hydroxy, optionally substituted aryl, optionally substituted heterocyclyl or OR^7a, SR^7a or NR^7aR^8a in which R^7a and R^8a are either the same or different and selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted aryl or optionally substituted hetercyclyl; CN; $CH_2NR^9aR^{10}a$, $HCNOR^9a$ or $HCNNR^9aR^{10}$ in which R^9a and $R^{10}a$ are either the same or

different and selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted aryl or optionally substituted heterocyclyl; $OR^{11}a$, $SR^{11}a$ or $NR^{11}aR^{12}a$ in which $R^{11}a$ and $R^{12}a$ are either the same or different and selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted aryl or optionally substituted heterocyclyl or together form optionally substituted heterocyclyl; or $SO_2NR^{13}aR^{14}a$ in which $R^{13}a$ and $R^{14}a$ are either the same or different and selected from H or optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted aryl or optionally substituted heterocyclyl.

25. The method of Claim 20 or 21, wherein the 8-substituted quinoloneis of the



Ib

Formula Ib:

in which:

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety;

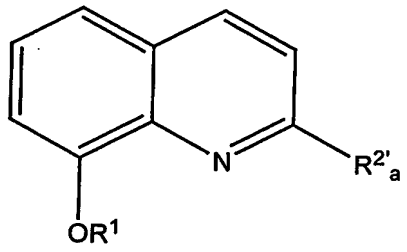
R^3 is either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl optionally substituted alkoxy, optionally substituted acyl, hydroxy, alkylamino, alkylthio, alkylsulphonyl, alkylsulphinyl, halo; SO_3H, amine, optionally substituted aryl, optionally substituted heterocyclyl, an anti-oxidant or a

targeting moiety; and

R^4b and R^5b are either the same or different and selected from H; optionally substituted C_{1-6} alkyl; optionally substituted C^{2-6} alkenyl; halo; an anti-oxidant; a targeting moiety, SO_3H; $SO_2NR^{13}aR^{14}a$ in which $R^{13}a$ and $R^{14}a$ are as defined in Formula Ia above; or $OR^{15}b$, $SR^{15}b$ or $NR^{15}bR^{16}b$ in which $R^{15}b$ and $R^{16}b$ are either the same or different and selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{1-6} acyl, optionally substituted aryl or optionally substituted heterocyclyl,

with the proviso that when R^1 and R^3 are H, then R^4b is not Cl and R^5b is not I.

26. The method of Claim 24, wherein the Ia is of the Formula of IIa:



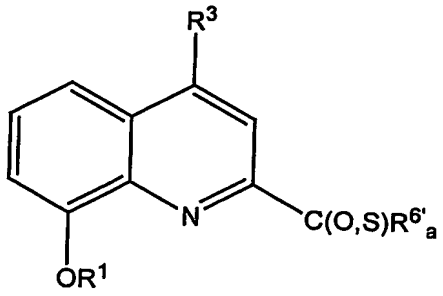
IIa

in which:

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety; and

$R^{2'}a$ is optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted aryl or optionally substituted heterocyclyl.

27. The method of Claim 24, wherein the Ia is of the Formula of IIIa:



IIIa

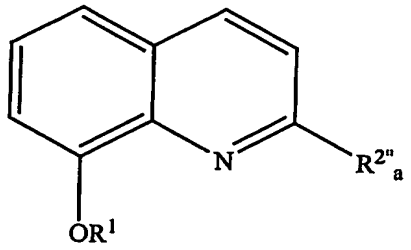
in which:

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety;

R^3 is either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl optionally substituted alkoxy, optionally substituted acyl, hydroxy, alkylamino, alkylthio, alkylsulphonyl, alkylsulphinyl, halo, SO_3H, amine, optionally substituted aryl, optionally substituted heterocyclyl, an anti-oxidant or a targeting moiety; and

$R^{6'}a$ is optionally substituted C_{1-6} alkyl, optionally substituted C2-6 alkenyl, hydroxy, $OR^{7'}a$, $SR^{7'}a$, $N_2R^{7'}aR^{8'}a$ or $NR^{7'}a\ R^{8'}a$ in which $R^{7'}a$ and $R^{8'}a$ are either the same or different and selected from H, optionally substituted C_{1-6} alkyl, optionally substituted aryl or optionally substituted heterocyclyl.

28. The method of Claim 20 or 21, wherein the 8-substituted quinolone is of the Formula IVa;



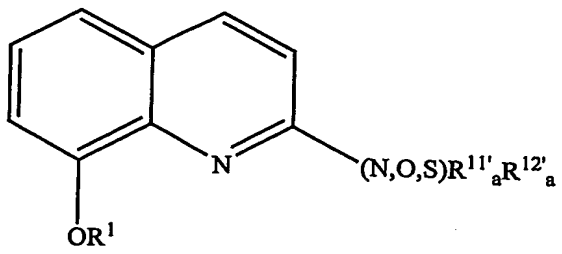
IVa

in which:

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety; and

$R^{2"}a$ is CN; $CH_2NR^{9'}aR^{10'}a$, $HCNOR^{9'}a$ or $HCNNR^{9'}aR^{10'}a$ in which $R^{9'}a$ and $R^{10'}a$ are either the same or different and selected from H, optionally substituted C_{1-6} alkyl, optionally substituted alkenyl, optionally substituted aryl or optionally substituted heterocyclyl.

29. The method of Claim 20 or 21, wherein the 8-substituted quinolone is of the Formula Va;



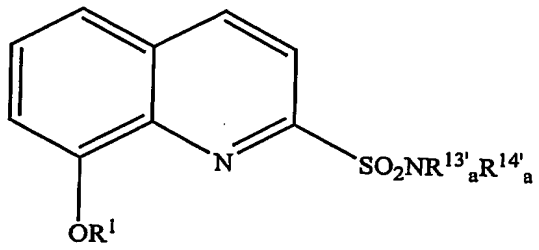
Va

in which:

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety; and

$R^{11}a'$ and $R^{12}a'$ are either the same or different and selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted aryl and optionally substituted heterocyclyl or together form optionally substituted heterocyclyl.

30. The method of Claim 20 or 21, wherein the 8-substituted quinolone is of the Formula VIa;



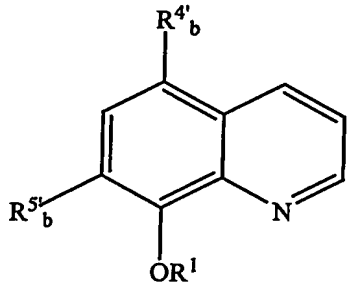
VIa

in which:

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety; and

$R^{13}a'$ and $R^{14}a'$ are either the same or different and selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted aryl or optionally substituted heterocyclyl.

31. The method of Claim 25, wherein the Ib is of the Formula of IIb;



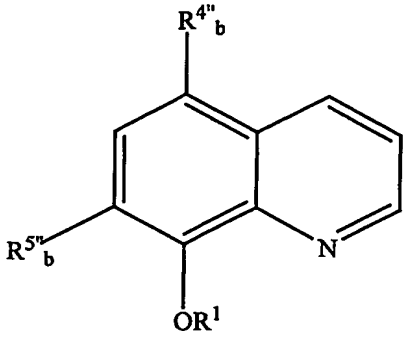
IIb

in which:

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety; and

R^4b' and R^5a' are either the same or different and selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, amine, SO_3H, optionally substituted aryl or optionally substituted heterocyclyl.

32. The method of Claim 25, wherein the Ib is of the Formula of IIIb;



IIIb

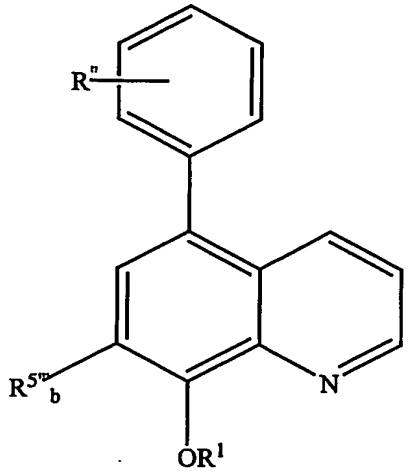
in which

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety;

R^4b'' is H or halo; and

R^5b'' is optionally substituted aryl or optionally substituted heterocyclyl.

33. The method of Claim 20 or 21, wherein the 8-substituted quinolone is of the Formula IVb;



IVb

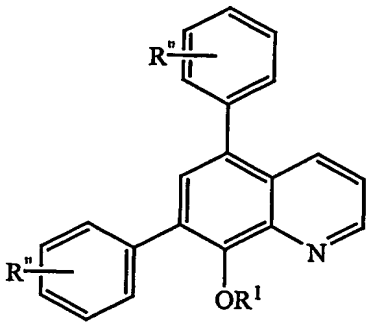
in which:

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety;

R" is C_{1-6} alkoxy, halo, C_{1-6} alkyl, C_{2-6} alkenyl or C_{1-6} haloalkyl; and

R^5b" is H or halo.

34. The method of Claim 20 or 21, wherein the 8-substituted quinolone is of the Formula Vb;



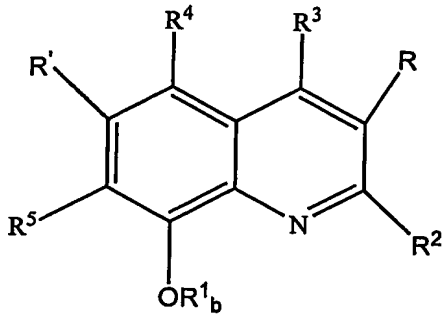
Vb

in which

R^1 is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted acyl, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant or a targeting moiety; and

R" is C_{1-6} alkoxy, halo, C_{1-6} alkyl, C_{2-6} alkenyl or C_{1-6} haloalkyl.

35. The method of Claim 20 or 21, wherein the 8-substituted quinolone is of the Formula VIb;



VIb

in which:

R^2 is H; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted aryl; optionally substituted heterocyclyl; optionally substituted alkoxy; an antioxidant; a targeting moiety; COR^6 or CSR^6 in which R^6 is H, optionally substituted alkyl, optionally substituted alkenyl, hydroxy, optionally substituted aryl, optionally substituted heterocyclyl, an antioxidant, a targeting moiety, OR^7, SR^7 or NR^7R^8 in which R^7 and R^8 are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl or optionally substituted heterocyclyl; CN; $CH_2NR^9R^{10}$, $HCNOR^9$ or $HCNNR^9R^{10}$ in which R^9 and R^{10} are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl or optionally substituted heterocyclyl; OR^{11}, SR^{11} or $NR^{11}R^{12}$ in which R^{11} and R^{12} are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl or optionally substituted heterocyclyl or together form optionally substituted heterocyclyl; or $SO_2NR^{13}R^{14}$ in which R^{13} and R^{14} are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl or optionally substituted heterocyclyl; and

R^3, R^4, R^5, R and R' are either the same or different and selected from H, optionally substituted alkyl, optionally substituted alkenyl optionally substituted alkoxy, optionally substituted acyl, hydroxy, alkylamino, alkylthio, alkylsulphonyl, alkylsulphinyl, halo, SO_3H, amine, optionally substituted aryl, optionally substituted heterocyclyl, an anti-oxidant or a targeting moiety, with the proviso that when R^1 to R^3, R and R' are H, then R^4 is not Cl and R^5 is not I; and

R^1b'' is optionally substituted C_{1-6} alkyl, optionally substituted aryl, optionally substituted aryl acyl, C_{1-6} alkyl acyl or optionally substituted heterocyclyl.

36. The method of Claim 22, wherein the neurological disorder is selected from sporadic or familial AD, Parkinson's disease, multiple sclerosis, amylotrophic lateral sclerosis, epilepsy, drug abuse or drug addiction (alcohol, cocaine, heroin, amphetamine or

the like), spinal cord disorders and/or injuries, dystrophy or degeneration of the neural retina (retinopathies) and peripheral neuropathies, such as diabetic neuropathy and/or the peripheral neuropathies induced by toxins, cardiomyopathy, AIDS dementia and HIV-1 induced neurotoxicity, atherosclerosis, cerebral ischaemia, cerebral palsy, cerebral tumour, chemotherapy-induced organ damage, cisplatin-induced nephrotoxicity, coronary artery bypass surgery, Creutzfeldt-Jacob disease and its new variant associated with "mad cow" disease, Down's syndrome, post-traumatic epilepsy, Friedrich's ataxia, frontotemporal dementia, glaucoma, glomerulopathy, hemochromatosis, hemodialysis, hemolysis, hemolytic uraemic syndrome (Weil's disease), hemorrhagic stroke, Hallerboden-Spatz disease, heart attack and reperfusion injury, Huntington's disease, Lewy body disease, intermittent claudication, ischaemic stroke, inflammatory bowel disease, macular degeneration, malaria, methanol-induced toxicity, meningitis (aseptic and tuberculous), motor neuron disease, multiple system atrophy, myocardial ischaemia, neoplasia, peri-natal asphyxia, Pick's disease, progressive supra-nuclear palsy, radiotherapy-induced organ damage, restenosis after angioplasty, retinopathy, senile dementia, schizophrenia, sepsis, septic shock, spongiform encephalopathies, subharrachnoid hemorrage/cerebral vasospasm, subdural hematoma, surgical trauma, including neurosurgery, thalassemia, transient ischaemic attack (TIA), traumatic brain injury (TBI), traumatic spinal injury, transplantation, vascular dementia, viral meningitis and viral encephalitis, dementia associated with Down's syndrome, amyotrophic lateral sclerosis, motorneuron disease, cataract, dementia with Lewy body formation, diffuse Lewy body disease, neurological diseases resulting from oxidative stress, such as, neurological disease resulting from diabetes, stroke and cardiovascular disease.

37. The method of any of any of Claims 20 or 21 or 22 wherein said 8-substituted quinolone is administered in conjunction with one or more pharmaceutically acceptable compounds used for treating a neurological disorders.

38. The method of Claim 37, wherein said compound is selected from phenserine, galantamine, or tacrine, Vitamin E or Vitamin C, flurbiprofen or ibuprofen, NCX-2216, 17-β-oestradiol and vitamin B12.

39. Use of any one or more of the agents of the Formulas I, Ia, Ib, IIa, IIIa, IVa, Va, VIa, IIb, IIIb, IVb, Vb and VIb in the manufacture of a medicament for the treatment and/or prophylaxis of a condition or disorder associated with or exacerbated by oxidative stress and with symptoms including cognitive impairment or memory loss.